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REVIEW

Rotavirus vaccination and herd immunity: an evidence-based review

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Abstract: Until recently, rotavirus was the most common cause of diarrhea in infants and young children with over 100 million cases and 400,000 deaths every year worldwide. Yet, its epidemiology is changing rapidly with the introduction of two rotavirus vaccines in the mid 2000s. Both vaccines were shown to be highly efficacious in prelicensure studies to reduce severe rotavirus disease; the efficacy being more pronounced in high- and middle-income countries than in low-income countries. Herd immunity – the indirect protection of unimmunized individuals as a result of others being immunized – was not expected to be a benefit of rotavirus vaccination programs since the vaccines were thought to reduce severe disease but not to decrease virus transmission significantly. Postlicensure studies, however, have suggested that this assumption may need reassessment. Studies in a variety of settings have shown evidence of greater than expected declines in rotavirus disease. While these studies were not designed specifically to detect herd immunity – and few failed to detect this phenomenon – the consistency of the evidence is compelling. These studies are reviewed and described here. While further work is needed, clarifying the presence of herd immunity is not just an academic exercise but an important issue for rotavirus control, especially in lower income countries where the incidence of the disease is highest and the direct protection of the vaccines is lower.

Keywords: rotavirus, vaccine, herd immunity, efficacy

Introduction

Rotavirus disease is changing quickly and dramatically with the recent introduction of two rotavirus vaccines. While this demonstrates, once again, the powerful effect that vaccines can have on the epidemiology, morbidity, and mortality of a disease, it also allows for revision of some of the preconceived notions of the disease. These revisions include the possibility that rotavirus may have accounted for more diarrheal illnesses than previously estimated, that heterotypic immunity – by yet unclear mechanisms – may be more broad than anticipated, and that there may be indirect protection (so-called herd immunity) from the vaccines. The data in favor – or against – that last notion is reviewed here.

Rotavirus disease

Rotaviruses are relatively complex 70-nm viruses that infect mature enterocytes in the small intestine, resulting in vomiting, diarrhea, and dehydration. The infected individual sheds large quantities of viral particles in the stool (about 10^{10}–10^{11}/mL, which greatly exceeds the infective dose of about 10 particles), facilitating transmission to others in close contact.[1] In fact, rotaviruses are among the most contagious viruses known.

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It is estimated that one infected person will generate about 20 new cases on average given contact with a maximum of susceptible human hosts.[2] Since rotavirus transmission is dependent on close person-to-person contact – unlike other diarrhea pathogens which are more dependent on common source contamination – improvements in sanitation have only a limited effect on spread of the infection. As a consequence, essentially every person in the world who is nonimmune will become infected and will do so at a young age. Thus, rotaviruses are the most common cause of diarrhea in infants and young children. In the United States (US), prior to the introduction of vaccines, all children would be infected before 5 years of age, resulting in 2.7 million episodes, 410,000 outpatient visits, 250,000 emergency department visits, and 60,000 hospitalizations annually.[3] Globally, the estimates are 111 million episodes, 25 million clinic visits, and 2 million hospitalizations.[4] Due to the variability in availability of medical care and presence of other conditions there is great disparity in mortality, with 20–60 deaths in the US and 440,000 deaths in the rest of the world.

Rotaviruses have eleven segments of double-stranded ribonucleic acid that encode for six structural and six nonstructural proteins. There are at least seven antigenic groups: A–G (human rotaviruses largely belong to group A). Serotypes are based on two surface proteins: viral protein-7 glycoprotein (G type) and viral protein-4 protease-cleaved hemagglutinin (P type); for P, a better system involves genotypes (denoted in brackets). The number of G and P types is constantly increasing; as of April 2011, 27 G and 35 serotypes had been confirmed.[5] Due to reassortment of the ribonucleic acid segments, all possible GP combinations could theoretically occur, yet some are more common, such as G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8].[6]

Primary rotavirus infection – mostly G1 – frequently confers protection against the infecting serotype, but protection against other types is infrequent and weak.[7] Secondary infections have a better chance of inducing heterotypic protection.[8] As a result, a child can have multiple infections. This was clearly shown in a study that prospectively followed 200 Mexican children from birth to 2 years of age.[9] Overall, one, two, three, four, and five infections were detected in 96%, 69%, 42%, 22%, and 13% of the children, respectively. The study also showed that each infection protected against the chances of a subsequent infection (which was usually caused by a different serotype) and, more importantly, decreased the severity of the episodes (after two clinical infections children had no more clinical infections). In addition, the authors demonstrated that while rotavirus natural infection was highly efficacious in preventing subsequent moderate-to-severe diarrhea (87%), it was less efficacious in the prevention of mild (73%) or subclinical (38%) infection. These principles would be later incorporated in the development of vaccine strategies.

Rotavirus vaccines

The high transmissibility of rotavirus and difficulty in controlling it by sanitation made development of a vaccine a priority. In 1998, a first rotavirus vaccine, called RotaShield® (Wyeth-Ayerst Laboratories, Madison, NJ) or rhesus-human rotavirus reassortant-tetravalent vaccine (RRV-TV), was licensed in the US. It was composed of four live attenuated viruses: the rhesus rotavirus strain MMU 18006 (of G3P5B[3] specificity) with rhesus-human reassortants with specificity for the three human G1, G2, and G4 types. In the US, three oral doses (at 2, 4, and 6 months of age) prevented 49% of all cases of rotavirus diarrhea, 80% of severe cases, 73% of medical visits, and 100% of dehydration.[10] Unfortunately, RRV-TV was soon discontinued when its use was found to be associated with intussusception.[11]

Despite this setback, 8 years later two new oral, live attenuated rotavirus vaccines were made available. RV5 (RotaTeq®; Merck and Co, Inc, Whitehouse Station, NJ) is a reassortant vaccine of bovine-human origin and contains five strains of G1–G4 and P1[8] specificities (on the G6P7[5] genetic backbone of the WC3 bovine rotavirus strain). A prelicensure clinical trial in various high- and middle-income countries (Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and US) showed that three doses (at 2, 4, and 6 months of age) prevented any (74%) and severe (98%) rotavirus disease, reducing clinic visits for rotavirus gastroenteritis by 86%.[12] In contrast, studies in low-income and lower middle-income countries in Africa (Ghana, Kenya, and Mali)[13] and Asia (Bangladesh and Vietnam)[14] showed lower efficacy, preventing only 39% and 48% of severe disease, respectively. The other vaccine, RV1 (Rotarix®; GlaxoSmithKline Biologicals, Rixensart, Belgium), is a monovalent vaccine derived from the human attenuated strain 89–12 of G1P[8] specificity, and recommended as a two-dose series (at about 2 and 4–6 months of age). A prelicensure clinical trial of RV1 in eleven Latin American countries (Argentina, Brazil, Chile, Colombia, Dominican Republic, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela) and Finland also demonstrated 85% efficacy to prevent severe rotavirus

diarrhea and hospitalization.[15] Similar to what was seen with RV5, a trial of RV1 in one low-income (Malawi) and one upper middle-income (South Africa) African country showed decreased efficacy to prevent severe rotavirus diarrhea (49% and 77%, respectively).[16] In 2006, RV5 was licensed in the US and RV1 was licensed in Latin America and Europe; in 2008 RV1 was licensed in the US. In 2007, the World Health Organization recommended that rotavirus vaccines (any) be included in immunization programs in the European Region and the Americas; in 2009 the recommendation was extended to all regions.[17]

What is herd immunity?

Immunologically speaking, vaccines can provide direct and indirect protection. Direct protection is that conferred to successfully immunized individuals (ie, received the vaccine and developed immunity). Indirect protection reflects the reduction in infection probability in unimmunized individuals as a result of others being immunized in the community. This indirect protection is also referred to as herd immunity, group immunity, or community immunity. The level of immunization required in a community for indirect protection to become evident varies with the disease and the vaccine (for a comprehensive review, see Fine[18]). It follows, then, that herd immunity can be demonstrated by detecting a level of protection higher than expected by vaccine coverage in a community, or by noting any level of protection among unimmunized subjects. The unimmunized subjects may be age-eligible children missed by the vaccine delivery system (likely to happen at the initial introduction of a program) or subjects that are age-ineligible (either too young or too old) for immunization. Due to concern for increased risk of intussusception in older infants, there is a very narrow age window for which rotavirus vaccines are indicated.[3] Since there is no catch-up schedule, this provided a unique opportunity in the early postlicensure years to study the effect of these vaccines on children who were still at some risk of rotavirus disease but were not age-eligible to receive the vaccines.

What could be the mechanism(s) of herd immunity?

One potential mechanism – well documented with oral poliovirus vaccine – is that of secondary immunization of contacts. Oral poliovirus vaccine strains replicate efficiently in the intestine of immunized children, are shed in the stool, and by fecal–oral contamination can "infect" (and immunize) unimmunized contacts.[19] This mechanism can theoretically occur with any live vaccine that replicates and is shed into the environment. Rotavirus vaccines are composed of live attenuated strains that replicate in the intestine and can be shed. RRV-TV was shed by approximately 50% of immunized children;[20] a clinical trial in Venezuela noted that 13% of placebo recipients developed diarrhea associated with an RRV-TV strain, presumably acquired horizontally from vaccine recipients.[21] Interestingly, even children who did not participate in that trial but lived in the same area had a significant decrease in rotavirus diarrhea (from 38% to 21%).[22] RV1 also is frequently shed by immunized children (approximately 50%–80%), mainly during the 7 days following the first dose; and transmission to contacts has been documented.[23–25] A unique study of 100 twin pairs in Dominican Republic estimated that the risk of household transmission of RV1 to the unimmunized twin (all asymptomatic cases) was 19%.[26] In contrast, shedding of RV5 has been detected at different frequencies (9% and 21% in healthy infants[27,28] and 55% in premature infants[29]), and even though transmission to unimmunized children has been documented, it seems to occur only occasionally.[30]

Another, perhaps more common, mechanism of herd immunity is through decreased exposure of unimmunized subjects to the pathogen as a result of decreased asymptomatic carriage (eg, as seen with *Haemophilus influenzae* type b[31] or *Streptococcus pneumoniae*[32] vaccines), or decreased clinical disease (eg, varicella[33] vaccine) and shedding of the pathogen by immunized children. Theoretically, any vaccine that prevents a disease normally transmitted from person-to-person can have this indirect effect. Rotavirus is transmitted most commonly from person-to person. A peculiarity of rotavirus natural infection, however, is that while it protects against subsequent clinical infection it does not prevent subclinical reinfection and virus circulation – a phenomenon consistently shown in cohorts of neonates,[34] young children,[9] and adults.[35] A vaccine would not be expected to perform better than natural infection – a principle reaffirmed when evaluation of an early candidate rotavirus vaccine (live attenuated bovine strain RIT 4237) found significant protection against clinical diarrhea (88%) but not against subclinical infection (nonsignificant 53% reduction).[36] Opposing this notion, though, one of the initial trials of RV1 found it efficacious in preventing any (73%) and severe (90%) rotavirus diarrhea, as well as subclinical infection (94% for the first season and 82% for two seasons).[37]

As this was only an isolated finding, the authoritative conclusion remained that rotavirus vaccines, despite being efficacious, would not be expected to significantly decrease the circulation of rotaviruses.[3,38]

What is the evidence for herd immunity following rotavirus vaccination?

MEDLINE was searched via PubMed using the keywords "rotavirus," "vaccine," and "herd immunity." Studies evaluating rotavirus disease since the introduction of the current rotavirus vaccines were retrieved. Reference lists of retrieved publications were also reviewed for relevant papers.

Tables 1–3 summarize data from studies reporting herd immunity for currently available rotavirus vaccines, arranged by country and vaccine used (RV5, RV1, or both). They all represent a time series in which – using various surveillance systems (single center, regional, or national) – rates of disease were compared for a few years before and after introduction of the vaccine (most studies exclude the transitional year of vaccine introduction). Since vaccines have been introduced relatively recently, the postlicensure comparator years were limited and many studies may be confounded by temporal changes in rotavirus activity. The variables investigated were sometimes general (eg, all-cause diarrhea), sometimes rotavirus-specific (if laboratory confirmation was available), and focused on different levels of severity (deaths, hospitalizations, emergency department visits, clinic visits). Except for one study with patient-specific vaccination data, vaccine coverage was usually estimated from external sources (sentinel sites, national registries, vaccine sales). More importantly, all studies were designed to evaluate vaccine effectiveness, not herd immunity. Herd immunity was suggested because either

Table 1 Studies reporting herd immunity associated with the use of RV5

Ref	Setting	Periods	Variables of interest	Evidence for herd immunity
40	US Nationwide NREVSS	2000–2006 vs 2007–2008	All ages RV-positive laboratory tests	For all ages, decrease in number (67%) and proportion (69%) of positive tests, greater than expected by estimates of vaccine coverage (~34%)
42	US Three counties NVSN	2006 vs 2008 and 2009	Age 0–35 mo RV hospitalizations	In 2008, decrease in RV hospitalizations for children 6–11 mo (87%), 12–23 mo (96%), and 24–35 mo (92%), greater than expected by vaccine coverage (77%, 46%, and 1%). In 2009, similar but less pronounced trends
43	US Nationwide SDI	2003–2006 vs 2007–2008	Age 0–4 y D and RV outpatient and inpatient visits	Decrease in all-cause D and RV visits for children <1 y (30% and 81%), 1 y (45% and 79%), and 2–4 y (35%–41% and 69%–78%), greater than expected by vaccine coverage (58%, 18%, and 0%). Decreases seen in the South, Northeast, and Midwest, less pronounced in the West
44	US Nationwide MarketScan	2001–2006 vs 2007–2008 and 2008–2009	Age 0–4 y D ED and outpatient visits RV hospitalizations	For 2007–2008, decrease in RV hospitalizations in children <1 y (81%), 1 y (72%), and 2–4 y (72%), greater than expected by vaccine coverage (73%, 64%, and 8%). Also, decrease in all-cause D hospitalization for all age groups. In 2008–2009, similar but less pronounced trends
45	US Nationwide HCUP	2000–2006 vs 2007 and 2008	Age 0–4 y D hospitalizations	In 2008, children 6–23 mo (age-eligible for vaccination) had 50% reduction in D hospitalization. Children 0–2 mo or 3–5 mo (too young) had 28%–42% reduction, and children 24–59 mo (too old) had 43%–45% reduction. Greater reductions in 2008 than 2007 for all age groups
46	US Nationwide NACHRI	2003–2006 vs 2007–2009	Age 0–4 y D hospitalizations RV hospitalizations	In 2007–2008, D and RV hospitalizations decreased for children vaccine-eligible: <1 y (47% and 85%) and 1 y (55% and 81%), as well as children too old to receive vaccine: 2–4 y (48% and 80%). In 2008–2009, similar but less pronounced trends
47	US Nationwide TRICARE Military	2003–2006 vs 2007–2009	Age 0–4 y D hospitalization RV hospitalization Child-specific RV immunization status	Immunized children had 88% overall decrease in RV hospitalization. For 2007–2008, unimmunized children also had a decrease in RV hospitalization: <12 mo (65%), 1 y (62%), 2 y (66%), and 3 y (64%). For 2008–2009, similar but less pronounced trends were noted. Children 4 y had nonsignificant declines for both years (43% and 10%)

(Continued)

Table 1 (*Continued*)

Ref	Setting	Periods	Variables of interest	Evidence for herd immunity
48	US, NY Statewide SPARCS	2003–2006 vs 2007–2008	Age 1 mo–18 y D hospitalizations RV hospitalizations	Reduction in D and RV hospitalizations for children most likely to have been immunized: 1–11 mo (37% and 84%) and 12–23 mo (45% and 86%), as well as children too old to be immunized: 24–35 mo (36% and 76%), 35–59 mo (37% and 88%), and 60 mo–18 y (9% and 70%)
49	US, PA Single center CHOP	2005–2006 vs 2007–2008	Age 0–18 y RV hospital visits	87% decrease, greater than expected for level of immunization (about 50% were not age-eligible for immunization and only a fraction of the rest were expected to have been immunized)
50	US, LA Single center CHNO	2004–2005 vs 2007–2009	Age 0–4 y RV ED visits and hospitalizations	Decrease in RV ED visits and hospitalizations for children <1 y (85%), 1 y (78%) and 2–4 y (41%), greater than expected by vaccine coverage (46%, 40%, and 11%)
51	US Nationwide NIS	2000–2006 vs 2008	All ages D hospitalizations RV hospitalizations	Decrease in D and RV hospital discharges in children 0–4 y (39% and 78%), 5–14 y (29% and 71%) and 15–24 y (8% and 65%). Older groups had nonsignificant decreases: 25–64 y (1% and 26%) and ≥ 65 y (−3% and 21%)
54	Australia Queensland QH	2000–2006 vs 2007 and 2008	All ages RV notifications	For 2007 and 2008, RV notifications decreased in children <2 y (vaccine age-eligible) by 53% and 65%, and in children 2–4 y (too old for immunization) by 65% and 56%. Vaccination coverage estimated >84% for <1 y
55	Australia Queensland QHAPDC	2000–2006 vs 2007 and 2008	All ages D hospitalizations RV hospitalizations	Decrease in D and RV hospitalizations for children 0–4 y for 2007 (18%–38% and 46%–57%) and 2008 (9%–18% and 34%–67%) and for 5–19 y (5% and 58%–61%). Older subjects had no reduction
56	Australia SA All hospitals	2005–2007 vs 2008–2010	Age 0–71 mo D hospitalizations RV hospitalizations	Decrease in D and RV hospitalizations for children vaccine eligible: 0–23 mo (42%–57% and 89%–90%), as well as children too old for immunization: 24–71 mo (42%–49% and 50%–83%)
57	Australia Victoria Single center	2003–2006 vs 2008–2009	Age 0–36 mo RV hospitalizations	74% and 81% decrease in RV hospitalizations among children 0–12 and 13–24 mo of age (age-eligible for immunization) and 61% among children 25–36 mo (too old to be immunized)

Abbreviations: CHNO, Children's Hospital, New Orleans; CHOP, Children's Hospital of Philadelphia; D, diarrhea; ED, emergency department; HCUP, Healthcare Cost and Utilization Project; LA, Louisiana; mo, months; NACHRI, National Association of Children's Hospitals and Related Institutions; NIS, Nationwide Inpatient Sample; NREVSS, National Respiratory and Enteric Virus Surveillance System; NVSN, New Vaccine Surveillance Network; NY, New York; PA, Pennsylvania; QH, Queensland Health; QHAPDC, Queensland Hospital Admitted Patient Data Collection; RV, rotavirus; SA, South Australia; SDI, SDI Health LLC; SPARCS, Statewide Planning and Research Cooperative System; US, United States; vs, versus; y, years.

the level of protection found was higher than expected by vaccine coverage or because protection was noted even among vaccine-ineligible subjects (ie, too old or too young). For all these reasons, every study reviewed has significant potential flaws in relation to herd immunity and thus should be interpreted with caution and in conjunction with other available data.

RV5

In the US, RV5 was introduced in 2006, followed by RV1 in 2008;[3] RV5 has been predominantly utilized (see Table 1). Building on prior experience with RRV-TV, the US developed a comprehensive system to monitor the impact of rotavirus vaccines. A series of surveillance programs was implemented at national, regional, and single site levels, including outpatient, inpatient, and laboratory-based data,

all assessing symptomatic cases of either all-cause diarrhea or rotavirus-specific diarrhea.

The National Respiratory and Enteric Virus Surveillance System is a passive voluntary network of laboratories reporting on rotavirus test results; while all ages are included, most tests are from children (clinical and epidemiological data are not collected). Soon after the first season following the introduction of RV5, National Respiratory and Enteric Virus Surveillance System data showed a >50% decrease in rotavirus activity as compared with the previous 15 seasons. This was more than expected by estimated vaccine coverage (about 34%), for the first time suggesting herd immunity.[39,40] One year later, an update of National Respiratory and Enteric Virus Surveillance System data confirmed these trends.[41] The New Vaccine Surveillance Network is a group of three countywide sites (Hamilton County, OH; Davidson County, TN; Monroe

Table 2 Studies reporting herd immunity associated with the use of RVI

Ref	Setting	Periods	Variables of interest	Evidence for herd immunity
59	Belgium Nationwide BSIPH	2005–2006 vs 2008	All ages RV laboratory reports	Overall decline 61.4%. Children <1 y and 1 y (vaccine-eligible) had 80.1% and 52% decrease. Children ≥2 y (too old) had 26% decrease
60	Belgium Single center GUH	1999–2006 vs 2006–2009	Age 0–5 y RV hospitalizations	In 2008–2009, children 0–2 y (vaccine-eligible) had 83% decrease and children 2–5 y (vaccine-ineligible) had 56% decrease in RV hospitalization
61	Belgium Nationwide Twelve hospitals	2004–2006 vs 2007–2008 and 2008–2009	Age 0–4 y RV hospitalizations	Children 2–24 mo (vaccine-eligible) had 65% and 80% reduction. Children 0–1 mo (too young) had 50% and 64% reduction. Children 25–59 mo (too old) had 20% and 64% reduction
62	Australia NSW Statewide	2001–2006 vs 2008	Age 0–5 y RV laboratory results D ED visits	Decrease in RV-positive cases and D ED visits among children age-eligible for vaccination (<15 mo: 83% and 21%) and children too old to be immunized (15 mo–5 y: 65% and 34%)
63	Australia NSW Single center	2001–2006 vs 2008–2009	Age 0–4 y RV hospitalizations	Decrease of 93% and 75% in RV hospitalizations among children 0–11 mo and 12–23 mo (age-eligible for immunization) as well as 30% among children 23–59 mo (too old to be immunized)
64	Mexico Nationwide MOH	2003–2006 vs 2008 and 2009	Age 0–59 mo D deaths	41% decline for children <11 mo (vaccine coverage 74% and 51% for one or two doses) and 29% decline for those 12–23 mo (vaccine coverage 4% and 2%). No effect in older children
65	Brazil Nationwide MOH	2004–2005 vs 2007 and 2008	Age 0–4 y D deaths	D mortality decreased 30%–39% in children <1 y (vaccine coverage 72%–77%) as well as 29%–33% in children 1–4 y (vaccine coverage 28%–38%)
66	Panama Nationwide MOH	2003–2005 vs 2007–2008	Age 0–4 y D hospitalizations	D hospitalizations decreased 15%–31% in children <1 y (vaccine coverage 63%–94%) and 26%–40% in children 1–4 y (vaccine coverage 25%). Greater effect seen during RV season (January–June) and in 2008 vs 2007
67	El Salvador 7 hospitals	2006 vs 2008	Age 0–4 y RV hospitalizations	84% decrease in RV hospitalization among children <1 y (vaccine coverage 76%), 86% among children 1 y (84% coverage) and 65% among children 2 y (too old for immunization). Children 3–4 y showed no consistent decline

Abbreviations: BSIPH, Belgian Scientific Institute of Public Health; D, diarrhea; ED, emergency department; GUH, Gasthuisberg University Hospital; mo, months; MOH, Ministry of Health; NSW, New South Wales; RV, rotavirus; vs, versus; y, years.

County, NY) prospectively conducting population-based surveillance in children < 36 months old with acute gastroenteritis. Comparison of New Vaccine Surveillance Network data before (2006) and after (2008) RV5 introduction showed a significant decrease in rotavirus hospitalization among children aged 6–11, 12–23, and 24–35 months (87%, 96%, and 92%, respectively), greater than the corresponding vaccine coverage in the area (77%, 46%, and 1%, respectively); the decreases were less pronounced but with similar trends for 2009.[42]

Third-party payer databases have also been used to estimate changes in medical claims due to rotavirus disease.

SDI Health LLC (Plymouth Meeting, PA) includes hospital (550 hospitals covering approximately 20% of US hospital visits) and outpatient encounters (from approximately 27,000 practitioners) for commercial payers and Medicaid. As compared with 2003–2006, in 2007–2008 there was a significant decrease in rotavirus-coded hospitalizations for children aged <1 year (81% for 58% vaccine coverage), 1 year (79% for 18% vaccine coverage), and 2–4 years (69%–78% for 0% vaccine coverage) for the South, Northeast, and Midwest US.[43] MarketScan® Commercial Claims and Encounters is a database of insurance claims derived from multiple private and public health plans

Table 3 Studies reporting herd immunity associated with simultaneous use of RVI and RV5

Ref	Setting	Periods	Variables of interest	Evidence for herd immunity
70	Austria Nationwide Eleven hospitals	2001–2005 vs 2008 and 2009	Age 0–60 mo RV hospitalizations	In 2008 and 2009, 87% and 79% decrease in children age-eligible (3–14 mo); 20% and 73% in children 15–32 mo (eligible starting 2009); 50% and 74% in children 0–2 mo (eligible at most for one dose); and 12% increase and 22% decrease in children 32–60 mo (too old to be immunized)

Abbreviations: mo, months; RV, rotavirus; vs, versus.

(Medicaid not included) with nearly 30 million enrollees (2 million of them children aged <5 years). Data were compared for before (2001–2006) and after (2007–2009) RV5 introduction. In 2007–2008, significant reductions in rotavirus hospitalizations were noted for children aged <1 year, 1 year, and 2–4 years (81%, 72%, and 72%, respectively), more than expected by vaccine coverage (64%, 23%, and 0%, respectively).[44] Similar to what was reported by others,[42] evidence for herd immunity was present but less pronounced in 2008–2009.

Hospital networks have also been used to pool cause-unspecified diarrhea and rotavirus-coded hospitalization data from large, representative segments of the US population. The Healthcare Cost and Utilization Project includes statewide hospitalization data from most US states (40 in 2008). Data from 18 such states (accounting for 49% of US children aged <5 years) were reviewed to determine diarrhea-related hospitalizations and compared 2007 and 2008 with 2000–2006 (no vaccine coverage data for the population were available). During the 2008 rotavirus season, children aged 6–23 months (age-eligible for vaccination) had a 50% reduction in diarrhea hospitalization; children aged 0–2 or 3–5 months (too young for vaccination) had a 28%–42% reduction, and children aged 24–59 months (too old for vaccination) had a 43%–45% reduction.[45] The Case Mix Comparative Data Program contains data from over 90 hospitals participating in the National Association of Children's Hospitals and Related Institutions. Data from 62 pediatric hospitals were analyzed to compare three seasons before (2003–2006) with two seasons after (2007–2009) RV5 introduction (again, no data on vaccine coverage were available).[46] For the 2007–2008 season, there were 85% and 81% reductions in rotavirus hospitalizations for those aged <1 year and 1 year (vaccine eligible) and an 80% reduction for those aged 2–4 years (too old for vaccination). Similar to other studies,[42,44] less pronounced reductions were noted for all age groups in 2008–2009, especially the 2–4 years group. US military dependents represent a well-defined stable segment of the population within the uniformed healthcare system. The M2 database was examined to identify children aged <5 years with a diagnosis of diarrhea or rotavirus disease for three seasons before (2003–2006) and two seasons after (2007–2009) RV5 introduction.[47] International Statistical Classification of Diseases and Related Health Problems-9 discharge codes were used to identify children with enteritis due to rotavirus. Unique to this study, data on patient-specific immunization status were available. Immunized children had an overall 88% reduction

in rotavirus hospitalization. Unimmunized children also experienced a decrease in rotavirus hospitalization: 65%, 62%, 66%, and 64% for children aged <1 year, 1 year, 2 years, and 3 years, respectively, for the 2007–2008 season; for the 2008–2009 season, reductions were less pronounced for the children aged <1 year and 1 year (55% and 45%, respectively) and nonsignificant for the children aged 2 years and 3 years (9% and −25%, respectively); for the children aged 4 years, reductions were nonsignificant for the two seasons (43% for 2007–2008 and 10% for 2008–2009). In the state of New York, hospitals are mandated to report to the Statewide Planning and Research Cooperative System. Ten hospitals consistently reporting rotavirus cases were selected and data from children aged <5 years (12% of statewide children) were analyzed to compare 2007–2008 (postvaccine) with 2003–2006 (prevaccine) seasons. Among children vaccine-eligible by age (1–11 and 12–23 months) there was a decrease in rotavirus hospitalization (84% and 86%, respectively), but also among children too old to be immunized (76% decrease for 24–35 months and 88% for 35–59 months); even children aged 60 months to 18 years of age had a 70% reduction in rotavirus gastroenteritis.[48]

The US national data have been mirrored by single center studies. The Children's Hospital of Philadelphia (Philadelphia, PA) reported that soon after the introduction of RV5 in their community, the hospital saw 87% fewer cases of rotavirus diarrhea in 2007–2008 compared with 2005–2006. They did not have data on vaccination status but indicated that at least 50% of their patients were age-ineligible and only a fraction of the rest was expected to have received the vaccine.[49] Children's Hospital (New Orleans, LA), as compared to baseline 2004–2005 data, reported an 85% and 50% decrease in rotavirus hospitalization for 2007–2008 and 2008–2009, respectively. The decrease was more pronounced for children aged <1 year (85%) and 1 year (78%) (vaccine-eligible) than 2–4 years (41%); for all groups declines were greater than the estimated vaccine coverage (46%, 40%, and 11%, respectively).[50]

As expected, most studies have focused on young children. However, several have looked into the effect of rotavirus vaccination on rotavirus disease among older children, adolescents, and adults who, by definition, have not been immunized. The Nationwide Inpatient Sample is a nationally representative database covering about 20% of US hospitals. Hospital discharge diagnoses of rotavirus gastroenteritis were reviewed for all age groups and data from 2008 (postvaccine) were compared with 2000–2006 (prevaccine). In 2008, when vaccine coverage was only

57% for children aged <1 year and 17% for children aged 1 year, significant decreases in cause-unspecified diarrhea and rotavirus-coded hospital discharges were noted for the groups aged 0–4 years (39% and 78%), 5–14 years (29% and 71%), and 15–24 years (8% and 65%); older groups (aged 25–64 years and ≥65 years) had nonsignificant reductions (1% and 26%, and −3% and 21%, respectively).[51] And finally, a study presented only in abstract form described a 48% reduction in rotavirus diarrhea among adults in Chicago seen in 2008–2010 as compared with 2006–2007.[52]

Australia introduced rotavirus vaccines into their publicly funded National Immunization Program in 2007, resulting in a rapid uptake (>80% in 2008).[53] While both vaccines are available, each state/territory selects one to be used; in the states of Queensland, South Australia, and Victoria, RV5 was selected. An early study found that, as compared with 2000–2006 (prevaccine), rotavirus notifications (all age groups) made to Queensland Health in 2007 and 2008 (postvaccine) decreased significantly (53% and 65%) for vaccine-eligible children aged <2 years as well as vaccine-ineligible children aged 2–4 years (65% and 56%).[54] The authors indicated that similar decreases were noted for older age groups but specific numbers were not provided. In a follow-up study,[55] the same group reviewed rotavirus hospitalization by age group as recorded in the Queensland Hospital Admitted Patient Data Collection – a system that gathers data for all public and private hospitals in Queensland – and compared 2000–2006 (prevaccine) with 2007 and 2008 (postvaccine). The study detected a significant decrease in diarrhea and rotavirus hospitalization for each of the first 5-year cohorts (0–4 years) in 2007 (18%–38% and 46%–57%) and 2008 (9%–18% and 34%–67%), as well as for 5–19 years in 2007 (5% and 61%) and 2008 (5% and 58%). Adults aged 20–64 years had no significant change and those aged ≥65 years had a four-fold increase in rotavirus hospitalization rate (even though that increase represented only minor changes in absolute numbers). In South Australia, as compared with 2005–2007 (prevaccine), in 2008–2010 (postvaccine) there was a significant decrease in diarrhea and rotavirus hospitalizations in vaccine-eligible children aged 0–23 months (42%–57% and 89%–90%), as well as vaccine-ineligible children aged 24–71 months (42%–59% and 50%–83%).[56] And, in Victoria, data on rotavirus hospitalization were collected at the Royal Children's Hospital (Melbourne, Australia) on children aged <3 years. Comparison of 2003–2006 with 2008–2009 data showed a 74% and 81% decrease in rotavirus hospitalizations among children aged 0–12 months and 13–24 months (age-eligible

for immunization), as well as 61% decrease among children aged 25–36 months (too old for immunization).[57]

RV1

RV1 was introduced in many Latin American and European countries in 2006 and in Australia in 2007 (see Table 2). Studies selected included one lower middle-income (El Salvador), two upper middle-income (Brazil and Panama), and two high-income (Belgium and Australia) countries. Two studies evaluated rotavirus-specific disease, while the others evaluated diarrhea-related hospitalization or death. While less specific than rotavirus disease to detect vaccine benefits, diarrhea is easier to assess (clinically and in the absence of laboratory tests) and is a more meaningful endpoint from the public health perspective. They all compared rates before and after the introduction of the vaccine (usually excluding the transitional year of vaccine introduction). In general, the studies detected a decline in rotavirus or diarrhea disease following RV1 introduction, mainly noticeable among children age-eligible for immunization and to a lesser degree among children too old to have been immunized.

In Belgium, RV1 was introduced in 2006 and RV5 in 2007. While the two vaccines were available, RV1 represented 95% of doses for 2006–2008.[58] Vaccine coverage increased quickly to 88% in 2007 and 90% in 2008. The Belgian Scientific Institute of Public Health (Brussels, Belgium) has been collecting data on laboratory-confirmed rotavirus infection (outpatient and inpatient) since 1999. An early study compared the number of rotavirus cases reported (all ages) for the period 2005–2006 (prevaccine) with 2008 (postvaccine). Overall, the number of cases declined by 61% and significant reductions were seen in all age groups. Children aged <1 year and 1 year (vaccine-eligible) had an 80% and 52% decrease. Children aged ≥2 years (too old to be immunized) also had a significant 26% decrease in rotavirus cases.[59] A second study was conducted by the Gasthuisberg University Hospital (Leuven, Belgium) by review of data on rotavirus hospitalizations among children aged 0–5 years and comparing the periods 1999–2006 with 2006–2009. For the overall study group increasing declines of 35%, 49%, and 66% were seen in 2006–2007, 2007–2008, and 2008–2009, respectively. Decreases were noted in all age groups, including those age-ineligible for vaccine. In 2008–2009 (2 years after vaccine introduction), children aged 0–2 years (vaccine-eligible) and 2–5 years (vaccine-ineligible) had an 83% and 56% decrease in rotavirus hospitalizations, respectively.[60] Finally, a larger study gathered data from twelve Belgian pediatric hospitals (comprising 30% of national pediatric beds) on rotavirus

hospitalizations occurring among children aged 0–4 years and compared 2004–2006 with 2007–2008 and 2008–2009. Significant decreases in rotavirus hospitalizations were noted for the overall group in 2007–2008 (58%) and 2008–2009 (77%). Children age-eligible for vaccination (2–24 months) had a 65% and 80% reduction, children too young to be immunized (0–1 month) had a 50% and 64% reduction, and children too old to be immunized (25–59 months) had a 20% and 64% reduction, respectively.[61]

In New South Wales, Australia, rotavirus-positive laboratory results in two public laboratories and diarrhea emergency room visits reported to the New South Wales Emergency Department Data were identified. As compared with 2001–2006, there was a decrease of 83% in laboratory-confirmed rotavirus cases in 2008 for children aged <15 months (age-eligible for vaccination) and 64% among children too old to be immunized (15 months to 5 years). There was also a decrease in emergency department diarrhea visits for both age groups (21% and 34%, respectively).[62] A subsequent study in the same area reviewed rotavirus hospitalizations at a single center (Children's Hospital at Westmead, Sydney, Australia). By 2008 the vaccine coverage was estimated at 85% for children aged <1 year. As compared with 2001–2006, there was a 75% decrease in rotavirus hospitalizations for children aged <5 years in 2008. The decrease was 93% and 75% for children aged <1 year and 1 year (eligible for immunization) and 30% for children 2–4 years (too old to be immunized).[63]

In Mexico, using data collected by the Ministry of Health, trends in diarrhea-related deaths in children aged 0–59 months were examined before (2003–2006) and after (2008 and 2009) the introduction of RV1. Vaccine coverage was estimated at 51%–74% among children aged <11 months and 2%–4% for children aged 12–23 months. Overall, there was a 41% decline in diarrhea mortality for children aged <11 months and 29% for those aged 12–23 months. For children aged 24–50 months, there was a nonsignificant 7% decline.[64] Similarly, in Brazil, using data collected by the Ministry of Health (expected to cover ≥85% of childhood mortality), diarrhea-related deaths for children aged <5 years were compared for 2004–2005 with 2007 and 2008. Vaccine coverage was estimated at 72%–77% for children aged <1 year and 28%–38% for children aged 1–4 years. A decrease in diarrhea-related deaths was noted in both years (2007 and 2008) and in both age groups: <1 year (30% and 39%) and 1–4 years old (29% and 33%).[65] In Panama, diarrhea-associated hospitalization was evaluated in children aged <5 years, comparing rates from 2003–2005 with 2007–2008, by review of a database maintained by the Ministry of Health. Children aged <1 year

(vaccine coverage 63%–94%) had a 15%–31% reduction in diarrhea hospitalization and children aged 1–4 years (vaccine coverage 25%) had a 26%–40% decrease.[66] In El Salvador data, were collected from children aged <5 years to assess rotavirus hospitalizations (from a network of seven hospitals nationwide) and compared 2006 with 2008 and 2009. Children aged <1 year in 2008 and 2009 (vaccine coverage 76% and 78%) had an 84% and 79% reduction in rotavirus hospitalizations, children aged 12–23 months of age (vaccine coverage 84% and 89%) had an 86% and 79% reduction, and children aged 2 years (vaccine coverage 0% and 84%) had a 65% and 46% reduction, respectively; children 3–4 years showed no ostensible reduction.[67]

Two additional studies, one from Brazil[68] and one from El Salvador,[69] mentioned a decrease in rotavirus disease among older unimmunized children, but age-specific data were not provided to confirm or quantify the difference.

RV1 and RV5

Austria implemented publicly funded universal mass vaccination with RV5 in mid 2007, switched to RV1 in 2008, and then back to RV5 in 2009 (see Table 3). Vaccine coverage was estimated at 87% in 2008. Since 1997 a surveillance system based on eleven sentinel hospitals (representing one-third of pediatric beds) was implemented to monitor rotavirus disease activity. Data on rotavirus hospitalizations among children aged 0–60 months were compared for 2001–2005 with 2008 and 2009. Children aged 3–14 months (vaccine age-eligible for both years) had decreases in hospitalization of 87% and 79% in 2008 and 2009, and children aged 15–32 months (eligible only the second year) had a 20% and 73% decrease, respectively. Children aged 0–2 months (might have had one dose at most) had a 50% and 74% decrease in 2008 and 2009. Children aged 32–60 months (too old to be immunized) had an increase of 12% in 2008 followed by a decrease of 22% in 2009.[70]

Hospital-acquired infections

Another impact of rotavirus vaccination not examined precensure is the potential effect of immunization on hospital-acquired infections. Three studies evaluated the impact of RV1 on hospital-acquired infections. In Austria,[71] surveillance data collected from sentinel hospitals found a 33% decrease (from 4.8% to 3.2%) in hospital-acquired rotavirus 2 years after the introduction of RV1. In Belgium,[61] analysis of data provided by twelve hospitals detected a 46% decrease (140 to 75 cases) in hospital-acquired rotavirus for the first year and a 76% decrease (140 to 33 cases) for the second year following

vaccine introduction. And in Australia,[63] a single-hospital (Children's Hospital at Westmead, Sydney) showed an 87% decrease (31 to four cases) in hospital-acquired rotavirus 2 years after vaccine introduction. One study evaluated RV5. This study was conducted in the US with data collected from a single hospital (Children's Memorial Hospital, Chicago, IL). As compared with 2003–2007 (prevaccine), in 2007–2008 and 2008–2009 (postvaccine), a 62% and 81% decrease in hospital-acquired rotavirus cases was noted (0.53 to 0.20 and 0.10 per 1000 patient-days, respectively). In comparison, the rates of hospital-acquired influenza and respiratory syncytial virus did not change, suggesting that vaccination rather than improvements in hygiene was responsible for the reduction in rotavirus transmission.[72] None of the studies provided information on the background vaccine coverage among the hospitalized children. Hence, while it seems plausible that the decrease in cases is the result of increasing rotavirus vaccination, it is impossible to tell whether it represents a direct effect of protection of exposed children, or an indirect effect of lesser circulation of rotavirus (herd immunity).

Evidence not supporting herd immunity

While there are numerous studies suggestive of herd immunity associated with the two rotavirus vaccines, several studies as summarized below did not demonstrate this effect (Table 4). Failure to detect herd immunity in some studies

may be due to low vaccine coverage in the community, performance of surveillance too early after the introduction of the vaccine, or measurement of nonspecific outcome variables (such as all-cause diarrhea).

In Austria – where both RV1 and RV5 are utilized – surveillance through eleven sentinel pediatric hospitals found that, as compared with 2001–2006 (prevaccine), in 2007–2008 (postvaccine) children likely immunized (3–20 months) and those who may have received one dose had a significant 74% and 42% decrease in rotavirus hospitalizations. In contrast, older children who were age-ineligible for vaccine (20–48 months) had a nonsignificant 8% increase in rates.[71] In Greece, both vaccines have also been in use since 2007 but, since they are not incorporated into the national immunization program, the rates of immunization remained low (<30%) at the time of a prospective, single-center (Children's Hospital P&A Kyriakou, Attica) study of rotavirus hospitalizations among children aged 0–5 years. Hospitalization rates in 2006–2008 (prevaccine) were compared with 2008–2010 (postvaccine). In children aged 0–11 months there was a significant 39% decrease in disease, while older children (1–4 years) had a nonsignificant 4% decrease.[73]

All-cause diarrhea-related hospitalizations were compared before (2003–2006) and after (2008 and 2009) RV1 introduction in Mexico using national data collected by the Ministry of Health on children aged <5 years. For the overall group, there was a reduction in hospitalizations by 11% and 40% in 2008

Table 4 Studies failing to detect herd immunity associated with rotavirus vaccination

Ref	Setting	Periods	Variables of interest	No evidence of herd immunity
71	Austria Nationwide Eleven hospitals	2001–2006 vs 2007–2008	Age 0–48 mo RV hospitalizations RV1 and RV5	Children 0–2 mo (likely received one dose) and children 3–20 mo (likely fully immunized) had a significant 42% and 74% decrease. Children 20–48 mo (vaccine-ineligible) had a nonsignificant 8% increase
73	Greece Single center	2006–2008 vs 2008–2010	Age 0–5 y RV hospitalizations RV1 and RV5	Low vaccine coverage (<30%). Children 0–11 mo (age-eligible) had a significant 39% decrease. Children 1–4 y (too old) had a nonsignificant 4% decrease
74	Mexico Nationwide MOH	2003–2006 vs 2008 and 2009	Age 0–59 mo D hospitalizations RV1	Children <12 mo had significant 25% (2008) and 52% (2009) decrease. Children 12–23 mo had nonsignificant 1% increase and significant 43% decrease. Children 24–59 mo had nonsignificant increase of 9% and 2%
75	Brazil Single center Sao Paolo	2004–2005 vs 2007–2008	Age 0–4 y RV hospitalizations RV1	Significant decrease in RV cases among children 0–11 mo (82%) and 12–23 mo (73%). Children 24–59 mo had a nonsignificant 29% decrease
76	Brazil Nationwide MOH	2002–2005 vs 2007–2009	Age 0–4 y D deaths D hospitalizations RV1	Significant decrease in D deaths and D hospitalizations for children <1 y (22% and 25%) and 1 y (28% and 21%). Children 2–4 y had a nonsignificant decrease of 4% and 7%
77	Nicaragua Statewide MOH	2003–2006 vs 2007–2009	Age 0–59 mo D episodes RV5	For all-cause D, during the RV season, children <12 mo (vaccine-eligible) had a significant 31% decrease, while children 12–59 mo (too old) had a 10% nonsignificant increase

Abbreviations: D, diarrhea; mo, months; MOH, Ministry of Health; RV, rotavirus; vs, versus; y, years.

and 2009, respectively. Significant decreases of 25% (2008) and 52% (2009) were noted for children aged <12 months. Children aged 12–23 months had a nonsignificant increase of 1% in 2008 and a significant decrease of 43% in 2009. Also, children aged 24–59 months (unvaccinated) had nonsignificant increases of 9% (2008) and 2% (2009).[74] Brazil also introduced RV1 in 2006. A single center (Hospital Sao Luiz, Sao Paulo) prospectively evaluated diarrhea and rotavirus visits in children aged <5 years for the periods 2004–2005 (prevaccine) and 2007–2008 (postvaccine). Overall, there was a 59% decline in rotavirus cases with significant declines among children aged 0–11 months (82%) and 12–23 months (73%). In contrast, children aged 24–59 months had a nonsignificant 29% decrease.[75] A second, larger study in Brazil reviewed a national database maintained by the Ministry of Health to identify diarrhea-related mortality and hospitalization after the introduction of RV1. The study compared data for children aged <5 years for the periods 2002–2005 (prevaccine) with 2007–2009 (postvaccine). Among children aged <1 year and 1 year, significant decreases of 22% and 28% in diarrhea-related deaths and 25% and 21% in diarrhea-related hospitalizations were detected. In contrast, children aged 2–4 years had a nonsignificant 4% and 7% decrease in diarrhea-related death and diarrhea-related hospitalization. Only one of four regions saw a significant decline in these parameters for children aged 2–4 years.[76] Finally, in Nicaragua, data reported to the Ministry of Health for the state of Leon were reviewed to determine all-cause diarrhea among children aged 0–59 months. RV5 was introduced in the area in 2006 and vaccine coverage for infants was estimated at 61%–82% during the study period. In 2007–2009, as compared with 2003–2006, children aged 0–11 months had a significant 31% decrease in all-cause diarrhea, while children aged 12–59 months (too old for immunization) had a nonsignificant 10% increase in diarrhea.[77]

Conclusion

The evidence regarding herd immunity associated with rotavirus vaccines is of poor quality because this effect was not anticipated and studies were not specifically designed to detect it. Present data are not suitable for formal meta-analysis, and further observational studies would be desirable. Studies used time series with short before and/or after observation periods, a situation vulnerable to temporal changes in rotavirus activity. Also, vaccine coverage was either unknown or inferred from external sources, which may or may not have been applicable to the study group. Yet, it seems highly compelling that many studies in different countries, under different conditions, and

using different surveillance systems have consistently found some evidence of herd immunity with similar results for both vaccines. If a real phenomenon, it may be explained by decreased circulation of rotavirus, a fact that was suggested by one prelicensure study but has not been evaluated postlicensure.[36] An alternative explanation is transmission of the vaccine virus from immunized infants to those unimmunized resulting in secondary immunization, as in the case of oral poliovirus vaccine. This also has support from the literature, especially for RV1 which has been shown to be shed at higher rates compared with RV5. While studies of both vaccines have shown evidence of herd immunity, the available literature does not allow comparison of the two vaccines to determine which might have a greater effect in this regard. This information would be important in lower income countries where the direct effect of the vaccines has been shown to be less than that in higher income countries. These data would be useful as countries consider which vaccine would be more cost-effective in a given setting. As vaccine coverage increases and direct protection is conferred to a larger segment of the population, the role of herd immunity becomes less relevant. Still, the phenomenon of herd immunity may remain evident among groups that will never receive the vaccine (adolescents and adults), countries with difficulty implementing an immunization program, or countries where the vaccine may be less efficacious.

Disclosure

The authors report no conflicts of interest in this work.

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